Support for the amendments to claim 6 is found in claim 14 as originally-filed. The amendment to claim 6, to replace "shown in" with "of", addresses the Examiner's objection to claim 6 at page 3 of the Office Action.

Support for the amendments to claim 24 is found in claim 7 as originally filed, and in the specification at page 4, line 34-page 5, line 2 and page 16, lines 23-24.

Support for the amendments to claims 28 and 30 is found at page 14, lines 25 through page 16, line 28, and in Figures 1-2 of the specification.

A substitute Declaration is submitted herewith to obviate the Examiner's objection to the Oath/Declaration as well as the Examiner's rejection of claims 5, 24 and 26-31 under 35 U.S.C. § 102(a) as unpatentable over Alderson et al. (Eur. J. Immunology, 24, 2219 (1994)).

The Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejected claims 5, 6, 24 and 26-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 22, 23, 29, 31-34, and 36 of copending application Serial No. 08/948,764. A terminal disclaimer is enclosed herewith to overcome this rejection.

The 35 U.S.C. § 102(b) rejection

The Examiner rejected claims 5, 24 and 26 under 35 U.S.C. § 102(b) as being anticipated by pages 1405 and 1419 of the Sigma Chemical Company catalog, the date of which the Examiner asserts is 1992 (the year is handwritten on the copy of the page of the Sigma Catalog entitled "Biochemicals, Organic Composition Diagnostic Reagents" Sigma Catalog provided to Applicant by the Examiner). The amendments to claims 5 and 24 render this rejection moot. Hence, withdrawal of the 35 U.S.C. § 102(b) rejection is respectfully requested.

The 35 U.S.C. § 112, second paragraph, rejections

The Examiner rejected claims 5, 24 and 26-31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

The amendment to claim 5, to replace "the" with "A", renders the § 112(2) rejection of claim 5 as it relates to the word "the" moot.

The amendment to claims 28 and 30, to delete the phrase "or a combination thereof", obviates the § 112(2) rejection of claims 28 and 30.

The amendments to claims 5 and 27 render the rejection of those claims related to the recitation of "protein" and "fragment" moot.

The Examiner asserts that it is not clear in claim 27 whether the extracellular domain of H4-1BB has SEQ ID NO:2 or whether the extracellular domain is contained within SEQ ID NO:2. One of ordinary skill in the art in possession of Applicant's specification would be apprised that SEQ ID NO:2 corresponds to full-length H4-1BB and that the extracellular domain of H4-1BB includes residues 1-186 (see Figure 2 and page 16, lines 17-22). Therefore, claim 27 is clear.

The Examiner alleges that the term "soluble" in claims 5, 24 and 26-31 is confusing as no type of solvent has been specified. It is Applicant's position that the metes and bounds of the term "soluble" in the context of claims 5, 24 and 26-31 would be readily understood by the art worker, as discussed below.

Claims 5, 24 and 26-31 are directed to a H4-1BB protein having SEQ ID NO:2 or a soluble form of that protein which is capable of specifically binding a cell membrane ligand for SEQ ID NO:2, e.g., a portion which comprises the extracellular domain (ECD) of H4-1BB. Figures 4(b)-(c) and 5(b)-(c) of Applicant's specification illustrate the interaction of membrane bound 4-1BB and a fusion protein referred to as 4-1BB/AP (see the specification at page 17, lines

22-23) with the ligand for 4-1BB. It is also disclosed that H4-1BB-AP, a fusion polypeptide which has the ECD of H4-1BB fused to alkaline phosphatase, is a soluble form of 4-1BB (page 15, lines 4-5). Page 16, lines 5-10 and 18-21 of the specification provides a description of the location of the signal sequence and the ECD of H4-1BB.

As further evidence that the term "soluble" in the context of a membrane protein is clear, the Examiner is respectfully requested to consider Armitage et al. (Eur. J. Immunol., 22, 2071 (1992)) and Pollock et al. (J. of Immunology, 150, 771 (1993)) (a copy of each is attached hereto). Armitage et al. report the use of a soluble fusion protein of CD40, a membrane-bound B cell protein, made up of the extracellular domain (ECD) of human CD40. Pollock et al. describe the production of 53A2, a monoclonal antibody generated against recombinant soluble 4-1BB (abstract), i.e., the mouse homolog of human 4-1BB. It is further disclosed that recombinant soluble 4-1BB protein (rs-4-1BBP) was encoded by DNA comprising the ECD of 4-1BB (page 772).

If one of ordinary skill in the art would understand the scope of the claim when read in light of the specification, then Applicant has complied with the requirements of § 112(2). In re Marosi, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); Morton Inst. Inc. v. Cardinal Chemical Co., 28 U.S.P.Q.2d 1190 (Fed. Cir. 1993); Miles Laboratories v. Shandon Inc., 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993), cert. denied, 510 U.S. 1100 (1994). Accordingly, the art worker in possession of Applicant's specification would readily understand the metes and bounds of the term "soluble" in the context of SEQ ID NO:2.

It is respectfully submitted that the claims are in conformance with 35 U.S.C. § 112, second paragraph, and so withdrawal of the rejections of the claims under § 112, second paragraph, is appropriate and is respectfully requested.

The 35 U.S.C. § 112, first paragraph, rejections

The Examiner rejected claims 5, 24, 26-27, 29, and 31 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for (a) a fragment of SEQ ID NO:2; (b) a fragment of an ECD of SEQ ID NO:2; (c) a fragment of residues 1-186 of SEQ ID NO:2; or (d) a protein encoded by a "combination" of SEQ ID numbers. The claims no longer recite the term "combination" thereby rendering the § 112(1) rejection as it relates to that term moot. As the remaining rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Claims 5, as amended, is directed to a recombinant H4-1BB protein or a soluble fragment thereof, wherein H4-1BB has SEQ ID NO:2 and wherein the soluble fragment is capable of specifically binding a cell membrane ligand for SEQ ID NO:2. Claim 24, as amended, is directed to a purified soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2 or a fragment of the extracellular domain which is capable of specifically binding a cell membrane ligand for SEQ ID NO:2. Claim 27, as amended, is directed to a recombinant soluble H4-1BB which is expressed from a DNA molecule encoding the extracellular domain of H4-1BB having SEQ ID NO:2 or a fragment of the extracellular domain which is capable of specifically binding a cell membrane ligand for SEQ ID NO:2.

It is Applicant's position that one of ordinary skill in the art in possession of Applicant's specification and knowledge generally available to the art would be apprised of how to identify fragments of a particular polypeptide that have a certain activity. For example, at page 16, lines 5-6 and 34-37 of the specification, Applicant describes the preparation of a fusion protein which contains the ECD of H4-1BB, i.e., it is a fragment of H4-1BB, for use in the identification of cells and tissues that express ligand for H4-1BB, and to modulate immune responses. To ascertain which amino acid residues of H4-1BB are in the fusion protein, the sequence of the oligonucleotides used to amplify this coding region (see lines 17-22 of page 16) can be aligned with the cDNA sequence of H4-1BB shown in Figure 2. Such an analysis indicates that residues 1-186 of H4-1BB contain the signal sequence and the entire ECD of H4-1BB.

As for identifying whether a particular fragment of H4-1BB binds to a cell membrane ligand, Applicant's specification discloses that H4-1BB ligand is expressed on mature B cells and macrophage, but not on T cells (page 11). Thus, B cells, macrophage, T cells, and/or cell lines derived therefrom, can be used to screen fragments of SEQ ID NO:2 for their ability to specifically bind to these cells. Alternatively, RNA is isolated from B cells, macrophage, and/or cell lines derived therefrom, and used to prepare an expression library that can be screened with H4-1BB to identify clones that express a H4-1BB ligand. Cells that express recombinant H4-1BB ligand can then be employed to identify which regions of SEQ ID NO:2 specifically bind to the ligand.

As further evidence that the art worker in possession of Applicant's specification and knowledge available to the art would be capable of identifying whether a portion of a certain polypeptide specifically binds to a cell membrane ligand, the Examiner is requested to reconsider the following documents. Armitage et al., (Eur. J. Immunol., 22, 2071 (1992)), Linsley et al., (Science, 257, 792 (1992)), Smith et al., (Science, 248, 1019 (1990)), Mathews et al. (Cell, 65, 973 (1991)), and Miyamura et al. (J. Clin. Invest., 98, 1809 (all of record).

Armitage et al. report that they used a biotin-labeled soluble fusion protein of CD40 (CD40 is a B cell membrane protein) and the Fc region of human IgGl (CD40.Fc) to identify a CD40 ligand on a murine thymoma cell line (i.e., T cells). Murine thymoma cells, which were selected for binding to the fusion protein, expressed a soluble protein that stimulated human and murine B cell proliferation, an activity which could be neutralized by precleaning the supernatants with immobilized CD40.Fc. Thus, the authors concluded that they had identified a source of membrane-bound and soluble CD40 ligand.

Linsley et al. discloses that B7 is a molecule on antigen presenting cells that binds to T cell surface molecules CD28 and CTLA-4. They report that a soluble fusion protein having the extracellular domain of CTLA-4 and Ig blocked the binding of B7 to CD28. Thus, the portion of CTLA-4 in the fusion protein binds to ligand.

To isolate the receptor for TNF-α and TNF-β, Smith et al. employed the radiolabeled ligand TNF-α as a probe to screen an expression library prepared from human lung fibroblasts. The cloned receptor, TNFR, was introduced into COS cells and shown to have the same ligand binding properties as the native receptor.

^{125}-activin was employed to screen COS cells transfected with cDNAs from AtT20 mouse cells to isolate an activin receptor (Mathews et al.). Moreover, in the Introduction section of the Mathews et al. paper, the authors note that a number of receptors, including the erythropoietin, IL-4, IL-6, IL-7, interferon-γ, GM-CSF and G-CSF receptors, have been cloned based on their ability to bind a labeled ligand following expression of a cDNA library in mammalian cells.

Miyamura et al. describe the preparation and screening of a series of deletion constructs encoding portions α-galactosidase A. Thus, it is clearly within the skill of the art worker to manipulate constructs, e.g., by deletion analyses, to identify constructs that encode a portion of a polypeptide and compare the activity of that truncated polypeptide, e.g., the ligand binding activity, to that of the full-length polypeptide.

Given Applicant's disclosure of the amino acid sequence of H4-1BB, i.e., SEQ ID NO:2, and the amino acid residues comprising the ECD of SEQ ID NO:2, and the skill of the art worker in the relevant art area, it is Applicant's position that the preparation and screening of fragments of SEQ ID NO:2 to identify regions of SEQ ID NO:2 that bind to a cell membrane ligand is well within the skill of the art.

In this regard, the Examiner is respectfully requested to consider Zhou et al. (Immunol. Lett., 45, 67 (1995), of record) which report the binding of a H4-1BB-AP fusion protein to a human B cell lymphoma (Daudi), a cell line which has higher numbers of H4-1BB ligand relative to normal B cells (page 73). Thus, a fragment of SEQ ID NO:2 which contained the ECD bound to cells having a ligand for SEQ ID NO:2.

Hence, Applicant's specification is fully enabling.

At page 5 of the Office Action, the Examiner also rejected claims 5, 24, 26-27, 29, and 31 under 35 U.S.C. § 112, first paragraph, alleging that the specification fails to provide a written description of the attributes shared by members of the genus made up of fragments of SEQ ID NO:2.

The description of an invention must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Univ. of Calif. v. Eli Lilly and Co., 119 F.3d 1559, 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). An adequate written description of claims drawn to a genus may be satisfied through a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show Applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099, 1106 (2001). While satisfaction of a "representative number" depends on whether one of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed, the description of a single species may adequately support a genus. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099, 1106 (2001).

Applicant discloses that fragments of H4-1BB having the ECD of H4-1BB may be used to detect and isolate a ligand for H4-1BB (H4-1BBL), as well as block H4-1BBL binding (see the specification at page 4, line 34-page 5, line 2 and page 5, lines 33-37; Figures 4-5; and claim 7). The amino acid sequence of H4-1BB is disclosed as SEQ ID NO:2 (Figure 2). A particular embodiment of the invention is disclosed as H4-1BB-AP, a fusion polypeptide which has the ECD of H4-1BB fused to alkaline phosphatase, which is a soluble form of 4-1BB (page 15, lines 4-5). Thus, Applicant clearly envisioned that fragments of SEQ ID NO:2 having a portion of the ECD could bind to the ligand for SEQ ID NO:2.

Therefore, the art worker in possession of Applicant's specification would recognize that Applicant was the inventor of H4-1BB comprising SEQ ID NO:2 and soluble fragments thereof which bind to the ligand for H4-1BB. Hence, Applicant's specification provides an adequate written description of the claimed invention.

Based on the remarks presented herein, it is respectfully submitted that the specification and pending claims are in conformance with 35 U.S.C. § 112, first paragraph. Thus, withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 12th day of July, 2001.

Dawn M. Poole
Name

Dawn M. Poole
Signature